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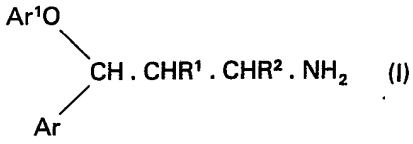
(54) 3-Aryl-3-aryloxypropylamines

(57) 3-Aryl-3-aryloxypropylamines of the general formula (I)



(I)

and their pharmaceutically acceptable acid addition salts, wherein R^1 and R^2 are hydrogen or lower alkyl, Ar is phenyl optionally substituted by one or more halogen or lower alkyl groups and Ar^1 is a phenyl group substituted by at least one nitro, amino or acylamino group, exhibit activity on the central nervous system, e.g. as antidepressants.

Certain of the chemical formulae appearing in the printed specification were submitted in formal form after the date of filing.

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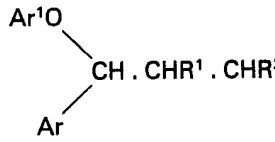
SPECIFICATION

3-Aryl-3-aryloxypropylamines

This invention relates to 3-aryl-3-aryloxypropylamines, to a process for preparing them, to their use and to pharmaceutical preparations containing them.

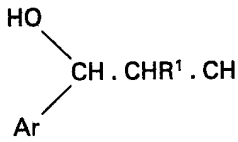
The present invention provides 3-aryl-3-aryloxypropylamines of the general formula (I)



(I)

and their pharmaceutically acceptable acid addition salts, wherein R^1 and R^2 are hydrogen or lower alkyl, Ar is phenyl optionally substituted by one or more halogen or lower alkyl groups and Ar^1 is a phenyl group substituted by at least one nitro, amino or acylamino group.

Compounds of the invention in which Ar^1 is a phenyl group substituted by one or more nitro groups may be prepared by a process which comprises reacting an anion of an alcohol of general formula (II)



(II)

(where Ar, R^1 and R^2 are as defined above) with a halo compound of general formula (III)

$$XAr^1 \qquad \text{(III)}$$

where X is fluorine and Ar^1 is a phenyl group substituted by one or more nitro groups. The reaction may be carried out in a dipolar aprotic solvent. Examples of dipolar aprotic solvents include dimethylsulphoxide, dimethyl formamide, hexamethylphosphoric triamide and sulpholane. Preferably the solvent is dimethylsulphoxide. The anion of the alcohol of general formula (II) is preferably formed by reacting the alcohol with potassium or sodium hydride or an alkyl or phenyl lithium (e.g. butyl lithium) in a compatible dipolar aprotic solvent. Preferably the alcohol is reacted with sodium hydride.

The process of the invention can be carried out at convenient temperatures e.g. 0 to 100°C (for example room temperature); there is generally no need to use reflux temperatures. Good yields of products are generally obtained in relatively short reaction times (e.g. within two to three hours).

Compounds of the invention in which Ar^1 is a phenyl group substituted by one or more amino groups may be prepared by reducing the compounds in which Ar^1 is a phenyl group substituted by one or more nitro groups. The reduction may, for example, be carried out catalytically. The amino substituents can be acylated, e.g. with acetic anhydride, to give compounds of the invention in which Ar^1 is a phenyl group substituted by one or more acylamino groups.

If in the processes described above the compound of the general formula (I) is obtained as an acid addition salt, such as a pharmaceutically acceptable acid addition salt or an acid addition salt such as an oxalate, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base a pharmaceutically acceptable acid addition salt may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with the conventional procedures for preparing acid addition salts from base compounds.

Examples of acid addition salts are those formed from inorganic and organic acids, such as sulphuric, hydrochloric, hydrobromic, phosphoric, tartaric, fumaric, maleic, citric, acetic, formic, methanesulphonic and p-toluenesulphonic acids.

The compounds of general formula (I) possess one or more asymmetric carbon atoms, depending upon the particular substituents. The compounds can therefore exist in various stereochemical forms. It will be realised that if the starting material of formula (II) is a mixture of isomers the product of formula (I) will also be a mixture of isomers which may be separated, if required, by standard procedures. If the starting material is a single isomer then the product will also be a single isomer.

The term "lower" as used herein means that the radical referred to contains 1 to 6 carbon atoms. The radical preferably contains 1 to 4 carbon atoms. Examples of lower alkyl radicals include methyl, ethyl, propyl and butyl. When R^1 and/or R^2 represents lower alkyl, the lower alkyl group is preferably a straight chain radical such as methyl, ethyl, n-propyl or n-butyl. When Ar^1 is substituted by acylamino the substituent can be, for example, acetamido.

The compounds of general formula (I) and their pharmaceutically acceptable acid addition salts, including the novel compounds of the invention, generally possess pharmacological activity. In particular the compounds exhibit activity on the central nervous system, e.g. as antidepressants, as indicated by one or more of the standard pharmacological test procedures such as the inhibition of 5-hydroxytryptamine uptake in rat brain slices and the modification of the effects of p-chloroamphetamine. For example, in the p-chloroamphetamine test, 3-(4-nitrophenoxy)-3-phenylpropylamine, a representative compound of the invention, was found to have an ED_{50} of 14.6 mg/kg.

The invention further provides a method of treating depression which comprises administering to a warm blooded mammal particularly a human, a therapeutically effective amount of a novel compound of the invention.

The invention also provides a pharmaceutical composition comprising a novel compound of the

invention in association with a pharmaceutically acceptable carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid form compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to 99, preferably 10—80% of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax, and cocoa butter. The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is with it. Similarly cachets are included.

Sterile liquid form compositions include sterile solutions, suspensions, emulsions, syrups and elixirs. The active ingredients can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances other compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by intramuscular, intraperitoneal or subcutaneous injection. In many instances a compound is orally active and can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in package form. The quantity of the active ingredient in a unit dose of composition may be varied or adjusted from 5 mg or less to 500 mg or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of the carrier where the compounds are in unit dosage form.

The following Examples illustrate the invention:

Example 1

3-(4-nitrophenoxy)-3-phenylpropylamine

A mixture of 3-hydroxy-3-phenylpropylamine (6 g, 40 mM), 50% sodium hydride dispersion (2 g, 40 mM) and DMSO (100 ml) was heated at 80° until homogenous, cooled to ambient temperature and treated with a solution of 4-fluoronitrobenzene (5.65 g, 40 mM) in DMSO (10 ml) with cooling. After 1 hour the reaction mixture was poured onto water (500 ml) and extracted with toluene (2×250 ml). The organic phase was washed with brine, dried and the solvent removed under reduced pressure. The residue was extracted with hot cyclohexane (4×250 ml), the solution charcoaled and the solvents removed under reduced pressure. The residue was taken up in ethyl acetate (100 ml) and treated with a solution of oxalic acid dihydrate (5 g) in ethyl acetate (200 ml). The resulting precipitate was removed by centrifugation, washed with several portions of ethyl acetate and dried in vacuo to give the title compound as the oxalate quarter hydrate (5.6 g) m.p. 173—5° (decomp).

Found: C, 55.6; H, 5.3; N, 7.3%
$C_{15}H_{16}N_2O_3 . C_2H_2O_4 . 1/4H_2O$ required:
C, 55.7; H, 5.1; N, 7.6%.

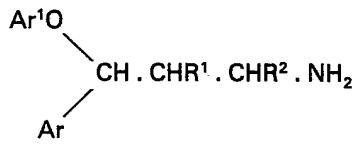
Example 2

3-(4-aminophenoxy)-3-phenylpropylamine

The title compound is prepared by hydrogenating a solution of 3-(4-nitrophenoxy)-3-phenylpropylamine at 1 atmosphere and ambient temperature over 5% palladium on charcoal until the theoretical uptake of hydrogen has occurred.

Claims

1. A 3-aryl-3-aryloxypropylamine of the general formula (I)



(I)

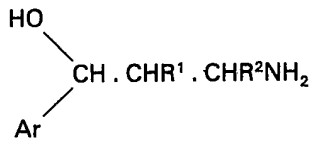
or a pharmaceutically acceptable acid addition salt thereof wherein R^1 and R^2 are hydrogen or lower alkyl, Ar is phenyl optionally substituted by one or more halogen or lower alkyl groups and Ar^1 is a phenyl group substituted by at least one nitro, amino or acylamino group.

2. A compound as claimed in Claim 1 wherein Ar^1 is nitrophenyl.

3. 3-(4-nitrophenoxy)-3-phenylpropylamine or a pharmaceutically acceptable acid addition salt thereof.

4. 3-(4-aminophenoxy)-3-phenylpropylamine or a pharmaceutically acceptable acid addition salt thereof.

5. A process for preparing a compound claimed in Claim 1 which comprises reacting an anion of an alcohol of general formula (II)



(wherein Ar, R^1 and R^2 are as defined in Claim 1) with a halo compound of general formula (III)

$$XAr^1 \qquad (III)$$

where X is fluorine and Ar^1 is a phenyl group substituted by one or more nitro groups, if required reducing the product to give a compound in which Ar^1 is a phenyl group substituted by one or more amino groups and if required acylating the amino substituent or substituents to acylamino substituent or substituents, and, if desired, converting a free base of general formula (I) into a pharmaceutically acceptable acid addition salt thereof.

6. A process as claimed in Claim 5 wherein the anion of the alcohol of general formula (II) is formed by reacting the alcohol with potassium or sodium hydride or with an alkyl or phenyl lithium.

7. A process for preparing a compound claimed in Claim 1 substantially as hereinbefore described with reference to either of the Examples.

8. A compound as claimed in Claim 1 whenever prepared by the process claimed in any one of Claims 5 to 7.

9. A pharmaceutical composition comprising a compound claimed in any one of Claims 1 to 4 and 8 in association with a pharmaceutically acceptable carrier.

10. A compound claimed in any one of Claims 1 to 4 and 8 for use an an antidepressant.

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